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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,338	07/11/2003	Jin-an Jiao	TNA-005.04	8452

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EXAMINER	
XIE, XIAOZHEN	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,338	JIAO ET AL.	
	Examiner	Art Unit	
	Xiaozhen Xie	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-64* is/are pending in the application.

4a) Of the above claim(s) *62-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *030711,040102,051003, 060119*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1646, Examiner: Xiaozhen Xie.

The Information Disclosure Statement (IDS) filed 11 July 2003, 2 January 2004, 3 October 2005 and 19 January 2006 has been entered in full.

Applicant's election without traverse of Group I, claims 37-61, and species SEQ ID NO: 4, in the reply filed on 23 March 2006 is acknowledged.

Claims 37-64 are pending. Claims 62-64 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 37-61 are under examination.

Specification

The disclosure is objected to because of the following informalities:

The Application No: 10/293,417 is now abandoned. The first line of the specification should include updated cross-reference to related applications.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-61 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method for reducing tissue factor (TF) levels to treat cancer comprising administering an antibody capable of binding native human tissue factor, and contacting cancer cells expressing TF with the antibody or fragment, wherein the antibody or fragment has the binding specificity equal or greater than H36.D2.B7 [ATCC HB12255], and the antibody comprises a sequence that has at lest 70% identity to SEQ ID NO: 1, or comprises a sequence represented by SEQ ID NO: 4, or comprises hypervariable regions at lest 90% identity to SEQ ID NOs: 5-10 inclusive. What applicant has described in the specification is an isolated antibody, H36.D2.B7 [ATCC HB12255] which light chain variable region comprises CDRs represented by SEQ ID Nos: 5-7 inclusive, and heavy chain variable region comprises CDRs represented by SEQ ID Nos: 8-10, inclusive, or has an amino acid sequence of SEQ ID NO: 4, wherein said antibody is capable of binding native human tissue factor and inhibiting the binding of Factor X (FX) to TF or the TF:FVIIa complex. Applicant has not described other anti-TF antibodies, fragments or variants such as an antibody comprising a sequence that has at lest 70% identity to SEQ ID NO: 1, or comprising hypervariable regions at lest 90% identity to SEQ ID NOs: 5-10 inclusive, which possess the same property. There is no teaching regarding the relationship of structure to function, such as where and what

the changes of the molecule can lead to the recited binding specificity and inhibiting activity. Thus, the claims encompass a genus of molecules, which vary substantially in composition, and could have very different structural and functional characteristics from the antibody that Applicant has disclosed.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making of the claimed product, or any combination thereof. In this case, there is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of peptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the

method of isolation. Adequate written description requires more than a mere statement that is part of the invention and reference to a method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated antibody, H36.D2.B7 [ATCC HB12255] which light chain variable region comprises CDRs represented by SEQ ID Nos: 5-7 inclusive, and heavy chain variable region comprises CDRs represented by SEQ ID Nos: 8-10 inclusive, or has an amino acid sequence of SEQ ID NO: 4, but not the full scope of the claimed antibody variants or fragments, is adequately described in the disclosure.

Claims 37-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for reducing TF levels to treat a solid tumor that expresses TF comprising administering an isolated antibody, H36.D2.B7 [ATCC HB12255] which light chain variable region comprises CDRs represented by SEQ ID Nos: 5-7 inclusive, and heavy chain variable region comprises CDRs represented by SEQ ID Nos: 8-10 inclusive, or has an amino acid sequence of SEQ ID NO: 4, or an immunoactive antibody fragment thereof represented by Fab, F(v), Fab' or F(ab)2, wherein said antibody or fragment is capable of binding native human tissue factor and inhibiting the binding of Factor X (FX) to TF or the TF:FVIIa complex, does

not reasonably provide enablement for a method comprising administering any other antibodies or fragments, including an antibody comprising a sequence that has at lest 70% identity to SEQ ID NO: 1, or comprising a sequence represented by SEQ ID NO: 4, or comprising hypervariable regions at lest 90% identity to SEQ ID NOs: 5-10 inclusive. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are broad in that they encompass or require the use of an antibody or a fragment which is capable of binding native human TF for treating any type of cancer in a mammal, wherein the antibody comprising a sequence that has at lest 70% identity to SEQ ID NO: 1, or comprising a sequence represented by SEQ ID NO: 4, or comprising hypervariable regions at lest 90% identity to SEQ ID NOs: 5-10 inclusive, and wherein the fragment can be any portion of an antibody. The specification discloses an isolated antibody, H36.D2.B7 [ATCC HB12255] which light chain variable region comprises CDRs represented by SEQ ID Nos: 5-7 inclusive, and heavy chain variable region comprises CDRs represented by SEQ ID Nos: 8-10, inclusive, or has an amino acid sequence of SEQ ID NO: 4, wherein said antibody is capable of binding native human tissue factor and inhibiting the binding of Factor X (FX) to TF or the TF:FVIIa complex. The specification, however, does not provide any guidance for making or using antibody variants or fragments possessing the properties of H36.D2.B7 [ATCC HB12255], including binding specificity, inhibiting activity for FX or FVII/FVIIa binding to the complex and anti-coagulant activity as recited in claims 55-60. There is no teaching

in the specification as to what structural changes can be made to the molecule without loss of function, or that would destroy the characteristics of the molecule. Further, it is well known in the art that even minor changes in sequence can result in major changes in function, especially if the minor sequence change occurs within an active site or alters the overall conformation of the protein molecule. For example, Cacia et al. (Biochemidtry, 1996, Vol. 35, pp. 1897-1903) teach the effect on antigen binding of an isomerized Asp residue located in the CDRs of a recombinant monoclonal antibody. Cacia et al. found that changing Asp-L32 decreased the relative binding affinity for IgE significantly, whether the mutant residue was an ananine, glutamate or the isomerization variants of Asp (pp. 1901, see section Interaction of E25 variants with IgE, and Table 4). In addition, the claims read on using any fragment or portion of an antibody. Alberts et al. teach that the antigen-binding domain is made up of the light chain and heavy chain variable regions (The Cell, 2002, Garland Science, 4th edition, esp. pp. 161, Fig. 3-42). Similarly, do Couto et al. teach that both the light chain and heavy chain variable regions are generally required for the binding properties of an antibody (U.S. Patent NO: 6,309,636B1, see column 7, lines 32-34). Therefore, without teachings in the specification regarding the structures or data supporting the claims drawn to variants or fragments of the antibody, one of ordinary skill in the art would not know how to use the invention commensurate in scope with the claims.

Furthermore, the specification, were it enabling for a method of treating a solid tumor that expresses TF in cancer cells or in the intra-tumoral endothelial cells, would still not reasonably provide enablement for the treatment of all forms of cancer. The

instant claims encompass treating all forms of cancer. The specification teaches administering an antibody/cytotoxin or effector molecule conjugate to a mammal having tumor cells that express TF, e.g. pancreatic, ovarian, or small lung cell carcinoma (pp. 20, 2nd paragraph, and pp. 21, last paragraph). The specification further describes in Examples 9 and 10 that an anti-TF antibody exhibits anti-coagulant activity by blocking cell surface TF in TF-transfected MDA-MB 435 cells (human breast cancer) or in HT-29Lu3 cells (human colorectal cancer). The specification, however, does not provide support for anti-cancer effect of the antibody for any cancer, or providing guidance for using the antibody to treat cancer of all tissue origin. While the prior art (Edgington et al., 1993, U. S. Patent NO: 5,223,427) teaches the same antibody for the use of treating a patient having tumor cells that express TF on their surface, such as carcinoma of breast and lung, it fails to provide compensatory guidance. Cancer encompasses neoplasm with many causes, striking many tissues, and with many different outcomes. Without further guidance, the artisan would not be able to predict what types of cancers could be treated using the claimed antibody. Thus, it would require undue experimentation for the artisan to practice the invention as broadly claimed. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification.

Due to the large quantity of experimentation necessary to generate the nearly infinite number of anti-TF antibody variants and fragments, recited in the claims and screen same for binding specificity to native human tissue factor and inhibiting activity of Factor X (FX) to TF or the TF:FVIIa complex, and determining their efficacy in treating

tumors of any tissue origin, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, and what types of tumors the antibody has anti-tumor effect, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on antibody structure and function, and the diversity and complexity of cancer from different tissue origin, the breadth of the claims which encompasses all types of tumors, and fails to recite any structural limitations for the antibody, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37, 38, 47 and 55-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 37 is indefinite for the recitation of "the mammal". There is insufficient antecedent basis for this limitation in the claim.

Claim 37 is indefinite for the recitation of "wherein the method further comprises contacting cancer cells expressing TF with the antibody or fragment to reduce the TF levels in the mammal to treat the cancer". It is not clear if the recitation is a further method step or if it is an alternative method.

Claims 38 and 55-57 are indefinite for the recitation of "the complex". There is insufficient antecedent basis for this limitation in the claim.

Claim 47 is indefinite for the recitation of "wherein the antibody comprises a sequence that has at least 70% sequence identity to SEQ ID NO: 1". SEQ ID NO: 1 is a nucleic acid sequence and an antibody comprises a polypeptide.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 37, 38, 42, 51-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Edgington et al. (1993, U. S. Patent NO: 5,223,427). The '427 patent teaches a method of treating a patient having tumor cells that express TF on their cell surface, such as carcinoma of breast and lung, by administering to the patient a anti-TF monoclonal antibody (MoAb) or its immunologically active portions of Ig molecules, e.g., Fab, Fab', F(ab')2, and F(v), linked to an anti-tumor agent to form an anti-tumor therapeutic composition (column 23, lines 3-11 and column, 20, lines 32-41). The '427 patent teaches that the MoAb binds to the native human TF (Fig. 6) and contains an immunologically effector IgG1 (Table 8). The '427 patent also teaches intravenous injection of the therapeutic MoAb-containing composition, which would expose cancer cells expressing TF with the antibody (column 23, lines 56-59). The '427 patent further teaches the MoAb inhibits coagulation by increasing the clotting time (Fig. 13) and is

capable of inhibiting the TF/VIIa complex by preventing FVII binding to, and FXa formation in bladder carcinoma cells treated with the MoAb, and the inhibition rates can reach more than 95% in an in vitro binding assay (Fig. 17). Therefore, the '427 patent anticipates the instant invention.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph. D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph. D.
June 8, 2006

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER